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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TURNER, SHARON L	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,792	MARGOLSKEE ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,25-33 and 36-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *17,25-33 and 36-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-23-05 has been entered.

2. The amendment filed 12-23-05 has been entered into the record and has been fully considered.

3. Estacion et al., and Okada et al., were removed as prior art in view of the amendment to the claims directing the structural limitation of SEQ ID NO:4.

4. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

5. Review of the prosecution history is now pertinent. The 112 2nd paragraph rejection previously of record (10-1-03) was withdrawn in view of Applicant's arguments that the skilled artisan would know suitable assays for assessing activation and inhibition of TRP8 as established in the prior art. This argument was persuasive as evidenced by the prior art newly cited in the Office Action of 10-4-04 as necessitated by amendment (the claims are newly drawn to TRP8 of SEQ ID NO:4, see Zucker et al., 102(e) US 2002/0164645). Zucker establishes suitable measurements for TRP8 activation and inhibition of taste receptor cell responses including for salty, sour, bitter and sweet sensations as well as methods for assessing compounds that modulate,

activate and inhibit such taste signaling responses. Applicant's were placed on notice that obviation of the new matter rejection may remove Zucker from the available prior art of record, and thereby remove the basis for withdrawal of the 112, second paragraph rejection of record. In that case, the rejection may be reinstated absent further evidence within the piror art that establishes well known assays for the assessment of TRP8 activation and/or inhibtion and how such correlates to the perception of a bitter as opposed to a sweet taste. While applicants have argued that such is within the skill of the art, no such evidence was presented in Applicant's response and the only such evidence/relevant reference found by the examiner is Zucker, now cited and relied upon for withdrawal of the rejection.

Instant amendment of 4-14-05 clarifies the invention in terms of the specification effective to receive the benefit of the noted priority date of 4-17-00 and removes Zucker as noted prior art. Applicants assert that guidance is provided to suitable assays as denoted within the specification, for assessing TRP8 activation as indicated via Hoffman, Liu and Parawitt with respect to TRPM5 (published in 2003) and for electrophysiological monitoring as in Gillo, Burnashev and Hu (published within 1994-1996). However, Hoffman Liu and Parawitt were not privy to the artisan at the time of invention in 2000, (i.e., the references were published in 2003). While Gillo, Burnashev and Hu evidence methods for assessing electrophysiological measurement including of calcium flux, the references are not on point to TRP8, do not clarify such measurements with respect to TRP8 activation and do not evidence adequate written description and enablement with respect to assessing measurement of a level of TRP8 activation at the

time of the priority document.

6. As a result of Applicant's amendment, all rejections not reiterated herein have been withdrawn.

7. Claims 17, 25-33 and 36-41 are pending.

Election/Restriction

8. Applicant's election with traverse of Group IV, to the extent of human TRP8 of SEQ ID NO:4, claim 17 in Paper No. 14 submitted 3-24-03, is acknowledged. The traversal is on the ground(s) that the claimed processes of Groups I-X are not independent and distinct as required by 35 USC 121. This is not found persuasive because as set forth in the restriction requirement of 2-25-03 the products and methods are distinct as claimed and directed to divergent compounds, steps, effects and outcomes. A search for any one product or method is not co-extensive with any other and search and examination of the multiple groups in a single application bears undue burden upon the Examiner.

The requirement is still deemed proper and is therefore made FINAL

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 17, 25-33 and 36-41 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility.

The specification teaches isolation of mouse mRNA and peptide expressed in taste receptor cells. Based on similar homology the mTRP8 was identified as a putative member of the known family of transient receptor potential channels, see spec., pp. 37-38. Using the cloned sequence the inventors sought to isolate and clone the human homolog and identified the corresponding peptide of SEQ ID NO:4 termed hTRP8. The specification notes that hTRP8 is homologous to mTRP8 as well as other TRP proteins and is expressed in taste receptor cells. hTRP8 demonstrates transient receptor potential as indicated via induced inward current upon the addition of Calcium, see paragraphs 104-105, and therefore hTRP8 falls within functions consistent with other TRP proteins.

However, as noted in Perez et al., 2002 (IDS 4-14-05) TRP proteins are recognized as functioning in many different ways in different cell types and even exist in one of three different forms, see in particular pp. 1169. As a family, TRP cells are not recognized as mediating taste reception and in fact the instant proteins are the only ones recognized as being expressed in taste receptor cells. Even as Perez acknowledges, the significance of expression and conductance in such cells is not resolved with respect to either bitter or sweet sensation and/or taste in general. In fact, no ligand has been demonstrated to be responsible for TRP activity. While Perez hypothesizes that the TRP channel in taste receptor cells functions for capacitative

calcium entry, even Perez acknowledges that this requires further confirmation, see in particular Discussion, 1173-74. The experimentation in Perez is largely similar to the experimentation at paragraphs 104-105 of instant specification evidencing conductance in thapsigarin treated oocytes upon addition of calcium. Yet Perez, evidences that this experimentation in not conclusive to confirm the function or role of TRP proteins in cells, let alone their particular function in any cell type. Accordingly, the specification fails to set forth a specific and substantial utility that evidences completion of an invention.

The use of the peptides in screening studies is not specific or substantial because the placement of the peptide in a family class does not complete the knowledge of the significance of the protein or how it may be used to cause benefit. While the specification provides evidence that the peptide may mediate capacitative calcium entry, the significance is not described such that the artisan can use it to provide for any particular effect that is reliably predicted. Even Perez notes that the placement or significance of expression within taste receptor cells is not enough to resolve whether or not the peptide mediates taste perception, transduction or any effect with respect to sweet or bitterness perception specifically. The mere ability to perform screening assays with any identified compound is not sufficient to provide utility for an invention for which no basis of predictable outcome is provided. Here the assays are merely a means for discovering the peptides functional significance either alone or in combination with any conceivable means of experimental manipulation using assays that detect TRP signalling. What is missing here is a basis or specific manipulation of reagents such that the artisan would arrive at a population of screened compounds

capable of providing a specific and/or substantial function, effect, and significance capable of use for providing a benefit. Yet here none is provided because any specific effect of TRP8 activity is presumption and/or speculation.

It is further noted that the assays are based upon measuring the level of intracellular calcium in the cell or change in membrane potential. Yet as Perez notes, taste receptor cells are subject to a host of primary and secondary signal transduction pathways even some of which mediate calcium flux via mechanisms other than the conductance demonstrated in thapsigarin treated oocyte preparations. Accordingly, calcium entry alone or the level of intracellular calcium are not necessarily linked in anyway to TRP8 activation or function and therefor the assays are not suitable to distinguish activation or inhibition of TRP8. Furthermore, the assay fails to denote whether it is the increase or decrease of any particular level that is desired to produce a particular effect. Again, such lack of description fails to evidence that the assays are capable of interpretable use when it is unclear even whether it is the increase or decrease of levels or positive or negative measure in membrane potential that is desired to provide for any sensation of bitter taste. It would not be expected that the opposite effects would carry same function and accordingly utility is not evidenced. Thus, the disclosed peptide merely constitutes a research reagent for further experimentation to discover its "real-world" use. The recited uses also do not constitute a well-established utility because the disclosed sequence is not readily recognized as providing for any specific and substantial effect that provides benefit. For these reasons there does not

appear to be either a specific and substantial, asserted utility or well-established utility for the claimed invention.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 17, 25-33 and 36-41 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the aforementioned, the following defects are noted with respect to enablement of instant invention as claimed.

The specification is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The amendment of 4-7-05 clarifies the invention in terms of the specification effective to receive the benefit of the noted priority date of 4-17-00 and removes Zucker as noted prior art. Applicants assert that guidance is provided to suitable assays as denoted within the specification, for assessing TRP8 activation as indicated via

Hoffman, Liu and Parawitt with respect to TRPM5 (published in 2003) and for electrophysiological monitoring as in Gillo, Burnashev and Hu (published within 1994-1996). However, Hoffman Liu and Parawitt were not privy to the artisan and the time of invention in 2000, (i.e., the references were published in 2003). While Gillo, Burnashev and Hu evidence methods for assessing electrophysiological measurement including of calcium flux, the references are not on point to TRP8 and do not clarify such measurements with respect to TRP8 activation. The artisan must be able to determine for any of the claims whether those response measured correspond to one of activation in comparison to the control. Clearly each measurement may yield opposite results indicating in contrast to activation, inhibition or represeion. Without guidance to delineate which measurements constitute "activation" from some other response, the artisan is unable to make and use the invention so as to assess compounds that induce a bitter taste.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed sequences without further undue experimentation.

In the response of 12-23-05, Applicants argue that the guidance of the specification teaches that activation of TRP8 by a bitter tastant results in extracellular

calcium entering the cells followed by down stream second messenger effects. Applicants argue measurement of receptor activation via membrane potential and calcium entry are routine as noted in Gillo, Burnashev, Hu, Dhallan, Misaka, and Altenhofen et al., and that accordingly one would be able to measure TRP8 activation by measuring calcium flux or the membrane potential of the cell. Applicants further argue that Bai and Chandrashekar teach measurements of receptor activation via calcium entry. Applicants assert that the Examiner has dismissed the references as they are not on point to TRP8 and assert that a proper analysis with the specification enables the artisan to measure TRP8 activation via the level of intracellular calcium in the cell or of cAMP or of phophodiesterase (cl. 29-30) or of a reporter gene or of membrane potential as in claim 37.

Applicant's arguments have been fully considered but are not persuasive. As noted in the utility rejection above, TRP8 function and/or activation is not definitely linked to induction of the perception of a bitter taste. The assay is required to provide such indication via comparable measurement of the level of intracellular calcium and membrane potential in the presence of a bitter tastant and as modulated via a putative compound. However, measurement of any level does not specify the level or change in level that is required of the claim so as to indicate activation. Moreover, there is no demonstration of TRP8 activity in response to any particular ligand or bitter tastant. While the specification asserts that TRP8 activation is associated with extracellular calcium entering the cell, this is not the only way that calcium may increase in the cell.

For example, Perez notes multiple other suitable pathways as do the alternative references of Gillo, Burnashev, Hu, Bai and Chandrashekar.

Calcium flux may be stimulated from both extracellular and/or intracellular stores, in response of a multitude of ligands, ion channels and/or second messengers. Accordingly there is no specific indication of any particular level that must be achieved nor is the calcium level determined under any particular condition where these multiple sources may be discerned from each other via any particular mechanism. For example, to assert transient receptor potential or capacitative calcium current via the oocyte calcium activated chloride channel in oocytes as indicated in the specification, experimentation was carried out under specific conditions in the presence of thapsigarin. Yet the claim is unable to distinguish any unrelated or alternative source of fluctuation. Therefore the measurement of calcium levels or of membrane potential alone may have little to nothing to do with any direct link to TRP8 activation. Moreover, such is not evidence to mediate perception of a bitter taste. Accordingly, the enablement rejection is maintained.

13. Claims 17, 25-33 and 36-41 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification describes a polypeptide sequence consisting of SEQ ID NO:r, which is shown to exhibit increased calcium flux into the cell when in contact with a compound that induces the perception of a bitter taste. The claims recite measuring

levels of TRP8 activation, yet the claims do not constitute any relationship for calcium or any other molecule which is indicated as one of activation. The measurements instead encompass all responses utilizing any of the different modes of measurement yet none is correlated to TRP8 activation or perception of a bitter taste. The instantly disclosed, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera directed at any means for assessing TRP8 activation without disclosure of what measurements indicate activation. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of

a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Here only a single association is disclosed and the claims do not specifically delineate it.

The amendment of 4-7-05 clarifies the invention in terms of the specification effective to receive the benefit of the noted priority date of 4-17-00 and removes Zucker as noted prior art. Applicants assert that guidance is provided to suitable assays as denoted within the specification, for assessing TRP8 activation as indicated via Hoffman, Liu and Parawitt with respect to TRPM5 (published in 2003) and for electrophysiological monitoring as in Gillo, Burnashev and Hu (published within 1994-1996). However, Hoffman Liu and Parawitt were not privy to the artisan and the time of invention in 2000, (i.e., the references were published in 2003). While Gillo, Burnashev and Hu evidence methods for assessing electrophysiological measurement including of calcium flux, the references are not on point to TRP8 and do not clarify those measurements that constitute TRP8 activation. Accordingly, adequate written description is not provided.

Applicants argue in the 12-23-05 response that the claim correlates assay results such as intracellular calcium with TRP8 activation as supported in the specification including via means for assessing calcium concentration, cAMP concentration nerve

response assays sufficient for adequate written description support.

Applicant's arguments filed 12-23-05 have been fully considered but are not persuasive. In contrast to Applicants assertion, the change required is not defined. Measurement of a level alone does not indicate whether the change desired is one of an increase or one of a decrease. The claims do not define whether TRP8 activation is synonymous with an increased level of calcium or of a decreased level. While the artisan may be adept at performing experimentation or assays to assess the status or level of calcium or of the level of cAMP or to measure membrane potential, what is required of the claim is that the amount measured be indicative in comparison in the presence of the test compound to indicate whether the test compounds presence increased or decreased the activation of TRP8 and thereby the perception of a bitter taste. Notwithstanding the lack of evidence that TRP8 is linked directly to the perception of a bitter taste, the assay fails to distinguish the requirements indicative of a compound that induces the perception of a bitter taste as assessed via measuring the level of intracellular calcium or the level of the membrane potential. The level required is not specified nor whether the level is increased or decreased in comparison to the cell in the absence of the test compound. Accordingly, written description is maintained.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 17, 25-33 and 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 and new claim 37 are directed to a method for identifying a compound that induces the perception of a bitter taste comprising "an increased level of activated TRP8." Yet the artisan cannot discern the metes and bounds of "increased (level of/activation of/activated) TRP8." While the specification sets forth that calcium influx upon ligand binding is associated with the perception of a bitter taste, such limitations cannot be read into the claims from the specification. Moreover, while dependent claims 24-36 provide for various methods of "measuring the level of TRP8 activation" the claims do not delineate those measurements that are of "activation" vs., for example a neutral response or inhibition. For example, while the art tends to support increased calcium influx, see below, the claims are not so limited. Just measuring calcium for example would not clarify that the levels measured were of increased flux and hence of activation. Accordingly the claims are in part incomplete to those measurements constituting activation. Thus, the metes and bounds of the claim recitations remain indefinite to one of skill in the art because the claims do not delineate those measuring responses that are deemed to be "activating" responses.

As previously argued by Applicants "an increase in the activation of TRP8 results in an influx of calcium into the taste cell and a corresponding neural stimulation of bitter taste. Alternatively, the ability of a compound to inhibit bitter tastant induced calcium influx results in inhibition of signal transduction mediated by TRP8. See Specification,

generally, at 5.5 "Screening Assays for Drugs and Other Chemical Compounds Useful in Regulation of Taste Perception", pages 15- 23.

Further support for the functional limitations of the presently claimed method for activation of TRP8 protein or nucleotide is described in the Specification as "the ability of a test molecules to modulate the activity of TRP8 may be measured using standard biochemical and physiological techniques...," see Specification at page 17, lines 12- 13. Also, the activation of the "cells expressing the TRP8 channel protein are exposed to a test compound or to vehicle controls (e.g. placebos)...the cells can be assayed to measure the expression and/or activity of components of the signal transduction pathway of TRP8, or the activity of the signal transduction pathway itself can be assayed", see Specification at page 17, lines 7-11.

The courts hold that "patents are written by and for skilled artisans" otherwise it would require every patent document to include a technical treatise for the unskilled reader. This requirement has been long rejected of patent disclosures. See S3 *Inc. v NVIDIA Corp.,* 259 F.3d 1364, 1371 (Fed. Ck. 2001) citing *Atmel Com. v Information Storage Devices, Inc.,* 198 F.3d 1374 at 1382. The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art. See *Vivid Technologies, Inc. v American Science and Engineering, Inc.,* 200 F.3d 795, 804 53 USPQZd 1289, 1295 (Fed. Cir. 1999).

These arguments have been fully considered but are not persuasive. Applicant's position is that the artisan would know how to measure "TRP8 activation" and that no further clarification need be provided. To the extent that the specification and prior art teach that calcium influx is a noted effect mediating bitter taste, (see also original rejection), the skilled artisan could at least surmise upon reading the specification that calcium ion influx would be considered an activator and that inhibition of this response would be considered an inhibitor. However, this is only upon reading the specification

into the claims which is not permitted. Applicant's have not pointed to any definition within the specification or prior art references that directs the artisan to those measurements constituting "activation of TRP8." The rejection of record notes that no definitive activity or means of measurement is specified by the specification or claims and no standard of such measurement is recognized in the prior art. The specification notes many standard biochemical and physiological techniques. For example p. 22-23 paragraph spanning teaches that :

"The ability of a test molecule to modulate the activity of TRP8 may be measured using standard biochemical and physiological techniques. Responses such as activation or suppression of catalytic activity, phosphorylation or dephosphorylation of TRP8 and/or other proteins, activation or modulation of second messenger production, including changes in cellular ion levels, association, dissociation or translocation of signaling molecules, or transcription or translation of specific genes may be monitored. In non-limiting embodiments of the invention, changes in intracellular Ca2+ levels may be monitored by the fluorescence of indicator dyes such as indo, fura, etc. In addition activation of cyclic nucleotide phosphodiesterase, adenylate cyclase, phospholipases ATpases and Ca2+ sensitive release of neurotransmitters may be measured to identify compounds that modulate TRP8 signal transduction. Further, changes in membrane potential resulting from modulation of the TRP8 channel protein can be measured using a voltage clamp or patch recording methods."

Hence, it is clear that the specification and claims are intended to encompass more, i.e., other assays indicative of activation or inhibition. However, the specifics of such other measurements and direction as to which ones are deemed activators vs. inhibitors is not provided by the specification or prior art. Moreover, this passage is directed to "modulation" of activity of TRP8. The activity may be one of activation or conversely inhibition, especially in light of Applicants amendment to the claims as newly directed to induction and inhibition of the perception of a bitter taste and either an increase, decrease or neutral response. What is missing is a description of those

effects that constitute activation (other than Ca++ influx) vs. some other modulation of activity of TRP8 (i.e., inhibition). For example, would phosphorylation measurements of a particular protein constitute activation or inhibition? Dephosphorylation? While the specification does note that an increase in the activation of TRP8 results in an influx of calcium into the taste cell and that such is deemed to be indicative of a bitter taste, the claims are not so directed or limited to calcium influx and the specification is clear that other measurements are encompassed. Yet the specification, claims and prior art fail to teach which measurements other than calcium influx are indicative of 'activation' and the claims are not so limited. The specification is further clear that some of the responses activate while others inhibit. Thus, the claims cannot be considered only broad, but instead are indefinite because those activities which constitute activation vs. inhibition of TRP8 are not distinguishable or separately noted, and because no recognized means of ascertaining these differences is provided. Further the prior art does not apparently establish these specifics, particularly in light that TRP8 is not noted to share all functions with its other family members, see Estacion et al., and Okada et al., previously of record. The scope of the claim remains indefinite and incomplete, even to the skilled artisan.

The Examiner suggests that importation of the limitations of claim 24 into claim 17 and clarification that the measurement that indicates "activation" of TRP8 is a measurement of increased levels of intracellular Ca2+ in the cell, (in comparison as claimed) may expedite prosecution.

Applicants argue in the 12-23-05 response that the claim amendments correlates

the assay results such as increased levels of intracellular calcium with TRP8 activation as supported in the specification including via means for assessing calcium concentration, cAMP concentration nerve response assays sufficient to clarify the invention.

Applicant's arguments filed 12-23-05 have been fully considered but are not persuasive. In contrast to Applicants assertion, the change required is not defined, note specifically no "increased" level of calcium is required. Similarly no specific membrane potential is required of claim 37. Measurement of a level alone does not indicate whether the change desired is one of an increase or one of a decrease. The claims do not define whether TRP8 activation is synonymous with an increased level of calcium or of a decreased level. While the artisan may be adept at performing experimentation or assays to assess the status or level of calcium or of the level of cAMP or to measure membrane potential, what is required of the claim is that the amount measured be indicative in comparison in the presence of the test compound to indicate whether the test compounds presence increased or decreased the activation of TRP8 and thereby the perception of a bitter taste. Notwithstanding the lack of evidence that TRP8 is linked directly to the perception of a bitter taste, the assay fails to distinguish the requirements indicative of a compound that induces the perception of a bitter taste as assessed via measuring the "level" of intracellular calcium or "measuring" the membrane potential. It is not the act of measuring that is indicative, but a specific measurement or change in comparison. The level required is not specified, nor whether the level is increased or decreased in comparison to the cell in the presence or absence of the test compound.

Accordingly, indefiniteness is proper especially where the art would require more for distinguishing amongst the two, and the suitable assays may be distinguished for such measurement that is specific to the function of TRP8 and not of some unrelated mechanistic effect. Rejection is maintained.

Status of Claims

16. No claims are allowed.

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Thursday from 7:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached at (571) 272-0867.

Sharon L. Turner, Ph.D.
March 13, 2006

SHARON TURNER, PH.D.
PRIMARY EXAMINER
3-13-06